REMARKS

Claims 1, 9, 13, 15, and 19-24 are pending in the application and are at issue.

Claim 1, the sole independent claim, recites a medical therapeutic treatment for a human suffering from Alzheimer's disease by administering a therapeutically effective amount of a balanced ET_A/ET_B endothelin receptor antagonist recited in the claims. Claim 9 recites that the balanced ET_A/ET_B antagonist is bosentan. In particular, the present invention is *not* directed to a cure for Alzheimer's disease. A person suffering from Alzheimer's disease will not be freed from the disease by the present method. The present method *does* treat adverse effects or symptoms resulting from Alzheimer's disease by addressing the issue of a reduced blood flow to the brain caused by Alzheimer's disease. The present method overcomes the vasoconstriction associated with Alzheimer's disease and improves a blood flow in the brain. This difference between cure and treatment must be kept in mind when considering the patentability of the presently claimed method because statements in the Office Action appear to equate cure and treatment.

Claims 1 and 9 stand rejected under 35 U.S.C. §103 as being obvious over Hughes et al. U.S. Patent Publication 2003/0040534 ('534) in view of a Wu publication (Wu). Claims 13, 15, and 19-24 stand rejected under 35 U.S.C. §103 as being obvious over the '534 publication in view of Wu, and further in view of Woolf U.S. Patent No. 5,466,696 ('696). For the reasons set forth below, it is submitted that these rejections are in error and should be withdrawn.

THE '534 PUBLICATION

The '534 publication discloses one specific endothelin antagonist, wherein the (+) dextrorotatory atropisomer has a much higher potency than the (-) levorotary atropisomer or the racemate ('534 publication, abstract). The '534 publication also discloses that the compounds are antagonists of ET-1, ET-2, and/or ET-3, and are useful in the treatment of conditions associated with increased ET levels and *all* endothelin-dependent disorders ('534 publication, paragraph [0011]). The '534 publication then recites a myriad of conditions that may be treated using the disclosed endothelin antagonist of the '534 publication ('534 publication, paragraphs [0012] through [0018]).

The '534 publication provides data showing *in vitro* binding of the enantiomers of the compound. In particular, the '534 publication discloses that the disclosed compounds bind to endothelin A (ET_A) receptors. These receptors are expressed by CHO-K1 cell used in the test ('534 publication, column 5, paragraph [0034]). The '534 publication shows that the sole compound disclosed in the reference binds to ET_A receptor, but the reference discloses nothing more. The '534 publication also fails to tie this binding to *any*, let alone *all*, of the diseases and conditions set forth at paragraphs [0012]-[0018] of the reference. The diseases vary greatly in identity and etiology, i.e., from cancer, to skin disorders, to arthritis, to lupus and fibrosis, to sickle cell diseases, and beyond. The '534 publication therefore is no more than a bald prediction that the disclosed compound can treat each disease state cited in the reference.

The '534 publication states that the compound is an endothelin antagonist. The reference further discloses that the compounds "are antagonists of ET-1, ET-2, and/or ET-3", which essentially is the definition of an ET_B receptor antagonist (see Wu publication discussion below). The '534 publication also demonstrated binding of the compound to ET_A receptors, but this does not equate to the compound being a selective ET_A inhibitor. The reference fails to provide any tests with respect to ET_B bonding. Accordingly, no conclusion can be made as to which type of endothelin antagonist the compound of the '534 publication belongs.

THE WU PUBLICATION

The Wu publication is a review article that identifies and classifies various endothelin antagonists. The endothelin antagonists were classified using an arbitrary criteria based on selectivity of compounds for ET_A receptors over ET_B receptors (Wu publication, page 1654, left column). Wu also discloses the following in the Introduction, at page 1653:

> "There are two distinct types of endothelin receptors cloned: the ET-1 selective ET_A receptors (binding ET-1 >> ET-2 ~ ET-3) primarily found on vascular smooth muscle and responsible for vasoconstriction; and the non-selective ET_B receptors (binding ET-1 ~ ET-2 ~ ET-3) primarily found in vascular endothelium and responsible for vasodilation."

The Wu publication also discloses that "[D]ue to the vasodilative properties of ET_B receptors" only a limited number ET_B selective antagonists were discovered (page 1658, right hand column). The Wu publication also states that ET_B selective compounds "are not beneficial" (page 1665, left hand column). This statement is incorrect, as discussed below.

The Wu publication also contains Table 1 at page 1665, listing ET_A and ET_A/ET_B antagonists that were under clinical development. Although all the compounds are ET_A or ET_A/ET_B antagonists, the compounds are being tested for a variety of different diseases and conditions, e.g., prostate cancer, congestive heart failure, myocardial infarction, hypertension, renal failure, and four other diseases. No single compound was being tested for more than three diseases. The Wu publication, in Table 1, therefore shows that *no single* endothelin antagonist (ET_A or ET_A/ET_B) is contemplated as being useful for all disease states. In addition, the table teaches that an ET_A antagonist and an ET_A/ET_B antagonist are being tested for the treatment of *different* diseases, except for congestive heart failure and hypertension. Accordingly, the Wu publication table shows that an ET_A antagonist is useful in the treatment of some diseases, whereas an ET_A/ET_B antagonist is useful in the treatment of others. Therefore, the efficacy of an ET_A antagonist *cannot* be equated to the efficacy of an ET_A/ET_B antagonist in the treatment of the same disease.

PROPER BASIS FOR AN OBVIOUSNESS REJECTION UNDER 35 U.S.C. §103

The U.S. Supreme Court in *Graham v. John Deere Co.*, 148 U.S.P.Q. 459 (1966) held that non-obviousness under 35 USC §103 is determined by: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the art; and, (4) inquiring as to any objective evidence of non-obviousness.

Furthermore, to establish a prima facie case of obviousness, the examiner must satisfy three requirements. First, as the U.S. Supreme Court very recently held in *KSR International Co. v. Teleflex Inc. et al.*, 127 S.Ct. 1727 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the

marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was *an apparent reason* to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to *identify* a *reason that would have prompted a person of ordinary skill in the relevant field to combine the elements* in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (emphasis added, *KSR*, *supra*). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. In *re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

To reach a proper determination under 35 U.S.C. §103(a), the examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all factual information, the examiner must then make a determination whether the claimed invention "as a whole" would have been obvious at that time to the person. Knowledge of applicants' disclosure must be put aside in reaching this determination, yet kept in mind in order to determine the "differences," conduct the search, and evaluate the "subject matter as a whole" of the invention. The tendency to resort to "hindsight" based upon applicants' disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the *facts* gleaned from the prior art. MPEP §2142.

The Supreme Court recently identified a number of rationales that may be used to support a conclusion of obviousness, consistent with the framework set forth in its decision in *Graham v. John Deere Co.* See *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1739-40 (2007). These and other representative rationales are described at MPEP §2143 (8th Ed., Rev. 6, Sept. 2007). Regardless of the supporting rationale the Patent Office must clearly articulate facts and reasons why the claimed invention "as a whole" would have been obvious to a person at ordinary skill in the art at least as of the claimed invention's effective

filing date. See *KSR Int'l*, 127 S.Ct at 1741 (citing with approval In *re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.")); see also MPEP §2143 ("The key to supporting any rejection under 35 USC §103 is the clear articulation of reason(s) why the claimed invention would have been obvious.").

The rational relied upon by the examiner apparently is as follows:

"B. Simple Substitution of One Known Element for Another To Obtain Predictable Results

To reject a claim based on this rationale, Office personnel must resolve the *Graham* factual inquiries. Office personnel must then articulate the following:

(1) a finding that the prior art contained a device (method, product, etc.) which differed from the claimed device by the substitution of some components (step, element, etc.) with other components;

(2) a finding that the substituted components and their functions were known in the art;

(3) a finding that one of ordinary skill in the art could have substituted one known element for another, and the results of the substitution would have been predictable; and

(4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

The rationale to support a conclusion that the claim would have been obvious *is that the substitution of one known element for another would have yielded predictable results* to one of ordinary skill in the art at the time of the invention. *If any of these findings cannot be made, then this rationale cannot be used* to support a conclusion that the claim would have been obvious to one of ordinary skill in the art." (Federal Register, Vol. 72, No. 195, page 57530, Oct. 10, 2007, emphasis added)

THE PENDING CLAIMS WOULD NOT HAVE BEEN OBVIOUS OVER THE COMBINATION OF CITED REFERENCES

The basis of the present rejection is that the '534 publication teaches an endothelin antagonist that can bind to ET_A receptors. The '534 publication further states that the disclosed compound is an antagonist of ET-1, ET-2, and/or ET-3. In addition, the '534 publication purports that the disclosed compound can treat "all endothelin dependent disorders," followed by a listing of a myriad of disorders, including the treatment of Alzheimer's dementia.

In addition, Wu discloses a large number of endothelin antagonists, classified as ET_A, balanced ET_A/ET_B, and ET_B receptor antagonists, and discloses disease states treated by endothelin antagonists, e.g., congestive heart failure, pulmonary hypertension, and renal failure. Wu fails to disclose the treatment of *any* dementias.

The examiner then reasons that it would have been obvious to substitute an ET_A/ET_B antagonist disclosed in Wu for the compound disclosed in the '534 publication in a medical therapeutic treatment of Alzheimer's Disease. Applicants traverse the examiner's reasoning because the substitution suggested by the examiner is not suggested by the combination of references and the results of the substitution would not have been predictable.

In particular, the '534 publication generalized the use of one specific endothelin inhibitor in the treatment of *any* endothelin related disorder. However, it is widely known that there are two types of endothelin receptors, ET_A and ET_B. ET_A receptors are potent vasoconstrictors; and ET_B receptors are well known as potent vasodilators. Hence, ET_A and ET_B receptors act opposite to one another. Supporting publications for these statements, and those that follow, were provided to the examiner in previously-filed Amendment "B". The examiner is also directed to page 12 of previously-filed Amendment "B" detailing differences that arise due to inhibition of ET_A receptors vs. inhibition of ET_B receptors. Thus, it is well known that inhibition of ET_A receptor or ET_B receptors, or both, can produce different effects.

The '534 publication discloses the use of CHO-K1 cell expressing ET_A receptors to show bonding of the disclosed compound (paragraphs [0033]-[0037]). The

reference therefore demonstrates binding of the disclosed compound to ET_A receptors, but not to ET_B receptors because no testing was performed for ET_B binding. Thus, it is unknown whether the disclosed compound has a greater binding affinity for ET_A or ET_B receptors, and as a result it is unknown whether the compound disclosed in the '534 publication is an ET_A, ET_B, or ET_A/ET_B receptor antagonist using the criteria of the Wu publication. Importantly, the '534 publication fails to state that the disclosed compound is an ET_A receptor antagonist, and provides insufficient facts to conclude that it is an ET_A receptor antagonist.

In addition, the '534 publication states that the disclosed compounds "are antagonists of ET-1, ET-2 *and/or* ET-3" (paragraph 11, emphasis added). It is also noted that non-selective ET_B receptors bind approximately equally to ET_1, ET_2, and ET_3, as disclosed in Wu (Introduction, page 1653). Therefore, the compound disclosed in the '534 publication may be an ET_B receptor antagonist based on the above statement in the '534 publication at paragraph 11.

Further, and importantly, the '534 publication has merely demonstrated *binding* of the disclosed compound to ET_A receptors. The reference provides no teaching as to whether the compound is an agonist or an antagonist of ET_A. Some compounds bind to an ET_A receptor and inhibit the receptor (antagonism); other compounds bind to an ET_A receptor and activate the receptor (agonism). Accordingly, the compound of the '534 publication may inhibit or may *activate* ET_A. The reference states that the compound is an endothelin antagonist, but provides no guidance, and it cannot be concluded that the compound inhibits ET_A. The reference further provides absolutely no guidance with respect to bonding to ET_B receptors, and then whether the compound should be classified as an ET_A, ET_A/ET_B, or ET_B receptor antagonist. The presently claimed compounds are known as ET_A/ET_B inhibitors and are useful in the treatment Alzheimer's disease symptoms and adverse effects.

The present claims recited mixed ET_A/ET_B antagonists, i.e., compounds that antagonize both ET_A and ET_B, e.g., bosentan of claim 9, and are useful in the treatment of Alzheimer's disease symptoms and adverse effects. The '534 publication fails to show that the compound is an ET_A antagonist, or to teach that the disclosed compound is a mixed ET_A/ET_B antagonist. In fact, the compound may be an ET_B antagonist. The reference therefore provides a person skilled in the art no incentive or apparent reason to select an

ET_A/ET_B receptor antagonist, and particularly bosentan, as a substitute for the endothelin receptor antagonist disclosed in the reference.

Furthermore, the '534 publication purports a treatment of the diseases disclosed in paragraphs [0012]-[0018]. This disclosure *lists more than 125 different classes and specific diseases and conditions* that are purportedly treated by the compound disclosed in the '534 publication. This disclosure in the '534 publication is no more than pure speculation and hoped for efficacy, and is unsupported by facts that all the disclosed diseases and conditions can be treated by the disclosed compound.

The Wu reference does not overcome the deficiencies of the '534 publication with respect to using an endothelin antagonist recited in the claims to treat Alzheimer's disease in a human. The Wu reference is relied upon for a teaching of various endothelin antagonists, and that bosentan is in clinical trials. First, it must be noted that bosentan is *not* in clinical trials relating to Alzheimer's disease. The fact that bosentan is in clinical trials is irrelevant with respect to the claims at issue. Further, as discussed above, Table 1 of the Wu publication lists nine other ET_A and ET_A/ET_B antagonists undergoing clinical trials for different diseases (none of which is related to dementia) and the ten different compounds are in clinical trails for different diseases, i.e., different antagonists treat different diseases.

Wu is a review article that teaches, identifies, and classifies various endothelin antagonists. In particular, Wu discloses 109 compounds, none of which are disclosed as treating *any* dementia. Notably, Wu does *not* teach or suggest the use of an endothelin antagonist in the treatment of Alzheimer's Disease or any other dementia. The '534 publication discloses the treatment of dementias no more than in passing. Therefore, a person skilled in the art, even with the '534 publication and the Wu reference before him, still would not have had any apparent reason to make the leaps in reasoning discussed above with respect to the '534 publication and thereby arrive at the presently claimed invention.

In particular, where is the incentive or apparent reason for a person skilled in the art to select a group of compounds (claim 1), and particularly bosentan (claim 9), from the 109 compounds of Wu, and use a claimed compound in *one* of the 125 different classes and specific disease disclosed in the '534 publication, with any reasonable expectation of

successfully treating Alzheimer's disease? This is especially true in view of Table 1 of the Wu publication, which shows the unpredictability in this art.

In the Office Action, the examiner makes apparently contradictory statements. First, relying upon a statement in Wu that selective ET_B antagonist compounds are not beneficial (Office Action, page 4), then stating that "positive responses are known from antagonizing both [ET_A and ET_B] receptors" (Office Action, page 8). At page 9, the examiner also states that "one skilled in the art would try the compound of Wu in *hopes* that the mixed ET_A/ET_B antagonist would be effective" to treat Alzheimer's dementia. Applicant disagrees with these statements.

The examiner's rejection is based on a reasoning that is a *fait accompli* that using *any* compound of Wu (total of 109) would be useful in treating any disease disclosed in the '534 publication (total of greater than 125). However, Table 1 of Wu shows the opposite. Individual endothelin antagonists are used to treat different diseases, with very little overlap. Individual selective ET_A antagonists are useful for treating different diseases, individual ET_A/ET_B antagonists also are useful for treating different diseases, and ET_A antagonists treat different diseases than balanced ET_A/ET_B antagonists.

The '534 patent also teaches that the disclosed compounds are antagonists of ET-1, ET-2, and/or ET-3, which more properly classifies the compounds as an ET_B antagonist. The information in the '534 publication is insufficient to classify the disclosed antagonist because only binding to ET_A is demonstrated.

Therefore, in view of (a) the vague teachings of the '534 publication with respect to how the disclosed compound should be classified, (b) the vast number of diseases and conditions, of different etiologies, disclosed in the '534 publication, and (c) the large number of different compounds disclosed in Wu, what would lead a person skilled in the art to select a particular endothelin antagonist (i.e., bosentan) or class of endothelin antagonist (i.e., ET_A/ ET_B antagonist) with any reasonable expectation of successfully treating Alzheimer's disease symptoms.

In addition, the statement that positive responses are not known for antagonizing both ET_A and ET_B receptors is traversed. The action of ET-1 and participation of its receptors varies in different organ systems. It has been shown, for example, that alveolar fluid clearance in the lung is reduced 65% by ET-1. It further was found that ET-1 induced inhibition of alveolar fluid clearance was completely prevented by the ET_B receptor antagonist BQ788, whereas the ET_A receptor antagonist, BQ123, had no effect (Berger et al., 2009, *Anesth Analg, vol 108*: pages 225-231). Therefore, it is clear that ET_B receptors do have positive role to play in various functions of the body.

It cannot be assumed, and the examiner has not supported, that the biological effects of ET_A receptor stimulation is similar to ET_B receptor stimulation, and that ET_A receptor stimulation is similar to ET_A/ET_B receptor stimulation. The role of each receptor is unique as provided by evidence that darunsentan, a specific ET_A receptor antagonist, has been found to be highly effective in the treatment of resistant hypertension, while *no* other ET antagonist has been found to have similar effect (Enseleit et al., 2008; *Expert Opin Investig Drugs vol 17*: page 1255-1263). Hence, there is unpredictability in the art, i.e., persons *a priori* have no reasonable expectation that substituting one ET antagonist for another will treat a specific disease.

Applicant also does not agree that ET_B receptors are not beneficial, and therefore they have no significance. The binding sites for ET-1 in rat brains with ischemia and in human brains with Alzheimer's disease were mapped by quantitative autoradiography. The ET-1 binding sites are decreased in the cerebral cortex of Alzheimer's disease and these binding sites could be blocked by BQ788 (ET_B antagonist) and not by BQ123 (ET_A antagonist) indicating the presence of ET_B receptors and not ET_A receptors (Kohzuki et al., 1995 *J. Cardiovasc Pharmacol, vol 26*, page S329-S331).

Although the '534 publication states that Alzheimer's dementia is associated with increased ET levels, prior studies showed that levels of ET-1 in the cerebrospinal fluid of patients of Alzheimer's disease is *lower* compared to controls (Yoshizawa et al., 1992 *Neuropeptides, vol 22*: page 85-88). Later reports showed increased expression of ET-1 in the astrocytes of the brain of Alzheimer's disease patients (Jiang et al., *Neuroreport vol 4*: page 935-937; Zhang et al., 1994 *J. Neurol. Sci. vol 122*, page 90-96). It also was found that

oligodendrocytes and endothelial cells of blood vessels of control and Alzheimer's disease cases do not show ET-1 immunoreactivity (Zhang et al., 1994 *J. Neurol. Sci. vol122* page 90-96).

All these studies show the unpredictability in the art of ET's and the results of inhibition of ET, in a particular organ, to treat a specific disease. This unpredictability coupled with the large number of compounds disclosed in Wu, and the vast number of diseases disclosed in the '534 publication, renders the present claims non-obvious over a combination of the '534 publication and Wu.

For these same reasons, the present claims would not have been obvious over the cited combination of references if the examiner relies upon an "obvious to try" rationale because (a) the unpredictability in the art, (b) the references do *not* provide a finite number of identified, *predictable* potential solutions (i.e., 125 diseases and 109 compounds) and (c) persons skilled in the art would not have had a reasonable expectation of success.

In summary, for all of the reasons set forth above, it is submitted that present claims 1 and 9 are patentable over a combination of the '534 publication and the Wu reference. Accordingly, this rejection of claims 1 and 9 under 35 U.S.C. §103 should be withdrawn.

With respect to the rejection of claims 13, 15 and 19-24 over a combination of the '534 publication, Wu, and the '696 patent, the examiner relies upon the '696 patent for a teaching that cholinesterase inhibitors are known to treat dementias. Claims 13, 15 and 19-24 recite preferred embodiments of the present invention. However, applicant does not rely upon the administration of a cholinesterase inhibitor to treat AD as the sole point of patentability.

Applicant relies upon all the features recited in claims 13, 15, and 19-24 *and* the claims from which they depend, including claim 1, for patentability. The '696 patent fails to overcome the deficiencies of the '534 publication and Wu with respect to treating a human suffering from Alzheimer's Disease with an endothelin antagonist. Therefore, claims 13, 15 and 19-24 are patentable over a combination of the '534 publication, Wu, and the '696 patent,

for the same reasons claims 1 and 9 are patentable over a combination of the '534 publication and Wu. Accordingly, the rejection of claims 13, 15, and 19-24 under 35 U.S.C. §103 should be withdrawn.

It is submitted that the claims are now in a form and scope for allowance. An early and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

Dated: February 19, 2009

Respectfully submitted,

By _____

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